EXCIPIENTS—THEIR ROLE IN PARENTERAL DOSAGE FORMS

Sandeep Nema
Pharmacia Corporation, Skokie, Illinois, U.S.A.

Ron J. Brendel
Mallinckrodt, Inc., St. Louis, Missouri, U.S.A.

Richard J. Washkuhn
Lexington, Kentucky, U.S.A.

INTRODUCTION

The term pharmaceutical excipient or additive denotes compounds that are added to the finished drug product for a variety of reasons. Most often excipients are major components of the drug product, with the active drug molecule present in a small percentage. Excipients also have been referred to as inactive or inert isngredients to distinguish them from the active pharmaceutical ingredients. However, in many instances excipients may not be as inert as some scientists believe. Several countries have restrictions on the type or the amount of excipient that can be included in the formulation of parenteral drug products due to safety issues. For example, in Japan, amino mercuric chloride, or thimerosal use is prohibited, even though these excipients are present in several products in the United States.

As defined in the *European Pharmacopoeia* (EP) 1997 and the *British Pharmacopoeia* (BP) 1999, "Parenteral preparations are sterile preparations intended for administration by injection, infusion, or implantation into the human or animal body" (1, 2). However, for the purposes of this article, only sterile preparations for administration by injection or infusion into the human body will be surveyed. Injectable products require a unique formulation strategy. The formulated product has to be sterile, pyrogen free, and in the case of solutions, free of particulate matter. No coloring agent may be added solely for the purpose of coloring the parenteral preparation. Preferably, the formulation should be isotonic, and depending on the route of administration, certain excipients may not be allowed. For a given drug, the risk of an adverse event may be higher or the effects may be difficult to reverse if it is administered as an injection versus a nonparenteral route, since the injected drug bypasses natural defense barriers. The requirement for sterility demands that the excipient be able to withstand terminal sterilization or aseptic processing. These factors limit the choice of excipients available to the formulator.

Generally, a knowledge of which excipients have been deemed safe by the Food and Drug Administration (FDA) or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product. However, there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug molecule, creating unforeseen potentiation or synergistic toxic effects. Regulatory bodies may view favorably an excipient previously approved in an injectable dosage form and will frequently require less safety data. A new additive in a formulated product will always require additional studies adding to the cost and timeline of product development.

In Japan, if the drug product contains an excipient with no precedence of use in that country, then the quality and safety attributes of the excipient must be evaluated by the Subcommittee on Pharmaceutical Excipients of the Central Pharmaceutical Affairs Council concurrently with the evaluation of the drug product application (3). Precedence of use means that the excipient has been used in a drug product in Japan, and will be administered via the same route and in a dose level equal to or greater than the excipient in question in the new application.

This chapter is a comprehensive review of the excipients included in the injectable products marketed in the United States, Europe, and Japan. A review of the literature indicates that only a few articles that specifically deal with the selection of parenteral excipients have been published (4–9). However, excipients included in other sterile dosage forms not administered parenterally, such as solutions for irrigation, ophthalmic or otic drops, and ointments, will not be covered.

Several sources of information were used to summarize the information compiled in this chapter (4–7, 10–14). Formulation information on the commercially available injectable products was entered in a worksheet. Tables presented in this chapter are condensed from this

worksheet. Each table is categorized based on the primary function of the excipient in the formulation. For example, citrates are classified as buffers and not as chelating agents, and ascorbates are categorized as antioxidants, although they can serve as buffers. This classification system minimizes redundancy and provides a reader-friendly format. The concentration of excipients is listed as percent weight by volume (w/v) or volume by volume (vol%). If the product was listed as lyophilized or powder, the percentages were derived based on the reconstitution volume commonly used. The tables list the range of concentration and examples of products containing the excipient, especially those that use an extremely low or high concentration.

TYPES OF EXCIPIENTS

Solvents and Cosolvents

Table 1 list solvents and cosolvents used in parenteral products. Water for injection is the most common solvent but may be combined or substituted with a cosolvent to improve the solubility or stability of drugs (15, 16). The dielectric constant and solubility parameters are among the most common polarity indices used for solvent blending (17, 18). Ethanol and propylene glycol are used either alone or in combination with other solvents in more than 50% of parenteral cosolvent systems. Surprisingly, propylene glycol is used more often than polyethylene glycols (PEGs) in spite of its higher myotoxicity and hemolyzing effects (19–22). The hemolytic potential of cosolvents is as follows (19):

$$\text{Dimethyl acetamide} < \text{PGE400} < \text{Ethanol} < \text{Propylene glycol} < \text{Dimethyloxide}$$

It is possible that the presence of residual peroxide from the bleaching of PEG or the generation of peroxides in PEG may result in the degradation of the drug in the cosolvent system. It is important to use unbleached and/or peroxide–free PEGs in the formulation.

Oils such as safflower and soybean are used in total parenteral nutrition products, where they serve as a fat source and as carriers for fat-soluble vitamins. The *U.S. Pharmacopeia* (USP) requirement for injectable oils is as follows:

A. Fixed oils (of vegetable origin)

- Saponification value (185–200)
- Iodine number (79–128). (*The Japanese Pharmacopoeia* (*JP*) recommends value between 79–137.)

Table 1 Solvents and cosolvents

Excipient	Frequency	Range	Example
Almond oil	1	ND	Poison Ivy Extract (Parke Davis)
Benzyl benzoate	3	20–44.7% w/v	Delestrogen® 40 mg/ml (Bristol Myers) 44.7% w/v
Castor oil	1	ND	Delestrogen® 20 mg/ml (Bristol Myers) 44.7% w/v
Cottonseed oil	2	73.6–87.4% w/v	Depo-Testadiol® (Upjohn) 87.4% w/v
N,*N*-Dimethylacetamide	2	6–33% w/v	Busulfex® (Orphan Medical) 33%
Ethanol	26	0.6–100%	Prograf (Fujisawa) 80 vol%, Alprostadil (Bedford Lab) 100%
Glycerin (glycerol)	12	1.6–70% w/v	Multitest CMI® (Pasteur Merieux) 70% w/v
Peanut oil	1	ND	Bal in Oil® (Becton Dickinson)
Polyethylene glycol			
PEG	5	0.15–50%	Secobarbital sodium (Wyeth-Ayerst) 50%
PEG 300	3	50–65%	VePesid® (Bristol Myers) 65% w/v
PEG 400	3	18–67 vol%	Busulfex® (Orphan Medical) 67%
PEG 600	1	5% w/v	Persantine® (Dupont-Merck)
PEG 3350	5	0.3–3%	Depo-Medrol® (Upjohn) 2.95% w/v
Poppyseed oil	1	ND	Ethiodol® (Savage)
Propylene glycol	29	0.2–80%	Ativan® (Wyeth-Ayerst) 80%
Safflower oil	2	5–10%	Liposyn II® (Abbott) 10%
Sesame oil	6	100%	Solganal Inj.® (Schering)
Soybean oil	4	5–20% w/v	Intralipid® (Clintec) 20%
Vegetable oil	2	ND	Virilon IM Inj.® (Star Pharmaceuticals)

ND, No data available.

- Test for unsaponifiable matter
- Test for free fatty acid
- Solid paraffin test at 10°C
- Acid value NMT 0.56 (*JP* only)

B. Synthetic mono-and diglycerides of fatty acids (which are liquid and remain so when cooled to 10°C)
- Iodine number (<140)
- Solid paraffin test at 10°C

The oils also are used to dissolve drugs with low aqueous solubility and provide a mechanism to slowly release drug over a long period of time. Deterioration of fixed oils, which leads to rancidity and production of free fatty acids, must be avoided in injectable products. Also the fixed oils or fatty acid esters must not contain mineral oil or paraffin which the body cannot metabolize.

Polymeric and Surface Active Compounds

Table 2 includes a broad category of excipients whose fun ction in formulation could be as follows:

1. To impart viscosity or act as suspending agents such as carboxy methyl cellulose, sodium carboxy methyl cellulose, acacia, Povidone, hydrolyzed gelatin, and sorbitol.
2. To act as solubilizing, wetting, or emulsifying agents such as Cremophor EL, sodium desoxycholate, Polysorbate 20 or 80, PEG 40 castor oil, PEG 60 castor oil, sodium dodecyl sulfate, lecithin, or egg yolk phospholipid.
3. To form gels such as when aluminum monostearate is added to fixed oil to form a viscous or gel-like suspension medium.

Polysorbate 80 is the most common and versatile solubilizing, wetting and emulsifying agent. Again, one must be concerned about the level of residual peroxides present in polysorbates and protecting them from air to prevent further oxidation (23). Polysorbate 80 is polyoxyethylene sorbitan ester of oleic acid (unsaturated fatty acid) while polyoxyethylene Polysorbate 20 is sorbitan ester of lauric acid (saturated fatty acid). Thus, stability differences could occur in the drug product formulated with Polysorbate 80 versus Polysorbate 20. One example is Neupogen® which when exposed to a high concentration of Polysorbate 20 exhibited substantially less oxidation than when exposed to a similar concentration of Polysorbate 80 (24).

Table 2 Solubilizing, wetting, suspending, emulsifying, or thickening agents

Excipient	Frequency	Range	Example
Acacia	2	7%	Tuberculin Old Test® (Lederle) 7%
Aluminum monostearate	1	2%	Solganal Inj.® (Schering) 2%
Carboxy methyl cellulose	4	0.50–0.55%	Bicillin® (Wyeth-Ayerst) 0.55%
Caboxy methyl cellulose, sodium	19	0.15–3.0%	Nutropin Depot® (Genentech) 3%
Cremophor EL[a]	3	50–65% w/v	Sandlmmune® (Sandoz) 65% w/v
Desoxycholate sodium	1	0.4% w/v	Fungizone® (Bristol Myers) 0.41% w/v
Egg yolk phospholipid	3	1.2%	Intralipid® (Clintec) 1.2%
Gelatin, Hydrolzyed	1	16% w/v	Cortone® (Merck) 16% w/v
Lecithin	8	0.4–1.2% w/v	Diprivan® (Zeneca) 1.2% w/v
Pluronic F-68	1	—	Fluosol® (Alpha Therapeutics)
Polyoxyethylated fatty acid	2	7–12% w/v	AquaMephyton® (Merck) 7% w/v Aquasol A parenteral® (Astra) 12%
Polysorbate 80 (Tween 80)	48	0.004–100%	Taxoterer® (Aventis) 100%
Polysorbate 20 (Tween 20)	9	0.01–0.4%	Calcijex® (Abbott) 0.4% w/v
PEG 40 castor oil[b]	1	11.5 vol%	Monistat® (Janssen) 11.5 vol%
PEG 60 castor oil[c]	1	20% w/v	Prograf® (Fujisawa) 20% w/v
Povidone (Polyvinyl pyrrolidone)	7	0.5–0.6% w/v	Bicillin®(Wyeth-Ayerst) 0.6% w/v
Sodium dodecyl sulfate (Na lauryl sulfate)	1	0.018% w/v	Proleukin® (Cetus) 0.018% w/v
Sorbitol	3	25–50%	Aristrospan® (Fujisawa) 50 vol%

[a]Cremophor EL, Etocas 35, polyethoxylated castor oil, polyoxyethylene 35 castor oil.
[b]PEG 40 castor oil, polyoxyl 40 castor oil, castor oil POE-40, Croduret 40, polyoxyethylene 40 castor oil, Protachem CA-40.
[c]PEG 60 hydrogenated castor oil, Cremophor RH 60, hydrogenated castor oil POE-60, Protachem CAH-60.

Table 3 Chelating agents

Excipient	Frequency	Range	Example
Calcium disodium EDTA[a]	9	0.01–0.1%	Wydase® (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	38	0.01–0.11%	Calcijex® (Abbott) 0.11% w/v
Sodium EDTA	1	0.20%	Folvite® (Lederle) 0.20%
DTPA[b]	1	0.04%	Magnevist® (Berlex) 0.04%

[a]EDTA = Ethylenediaminetetraacetic acid.
[b]DTPA = Diethylenetriaminepentaacetic acid; pentetic acid.

Chelating Agents

Only a limited number of chelating agents are used in parenteral products (Table 3). They serve to complex heavy metals and therefore can improve the efficacy of antioxidants or preservatives. Citric acid, tartaric acid and some amino acids also can act as chelating agents. There have been some misunderstandings concerning the use of EDTA (as calcium salt) as an approved injectable product in Japan. Currently in Japan, some drug products that contain calcium disodium EDTA are on the market and this excipient is also listed as an official excipient (see Table 11). An advantage of calcium EDTA over tetrasodium salt is that calcium EDTA does not contribute sodium and does not chelate as much calcium from the blood.

A complexing agent should not be used in metalloprotein formulations, where the protein subunits are held by the metal (25). The EDTA, in rare instances, can increase the oxidation rate due to binding of the EDTA–metal complex to protein, resulting in site-specific generation of radicals (26).

Antioxidants

Antioxidants are used to prevent the oxidation of active substances and excipients in the finished product. There are three main types of antioxidants:

1. *True antioxidants*: They act by a chain-termination mechanism by reacting with free radicals, e.g., butylated hydroxytoluene.
2. *Reducing agents*: They have a lower redox potential than the drug and get preferentially oxidized, e.g.,

Table 4 Antioxidants and reducing agents

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2–0.4% w/v	Novocaine® (Sanofi-Winthrop) 0.4% w/v
Ascorbate (sodium/acid)	8	0.1–4.8% w/v	Vibramycin® (Pfizer) 4.8% w/v
Bisulfite sodium	31	0.02–0.66% w/v	Amikin® (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	3	0.00028–0.03% w/v	Aquasol A® (Astra) 0.03% w/v
Butylated hydroxy toluene (BHT)	3	0.00116–0.03% w/v	Aquasol A® (Astra) 0.03% w/v
Cystein/Cysteinate HCl	3	0.07–1.3% w/v	Acthrel® (Ferring) 1.3% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan® (Endo Lab) 0.10%
Gentisic acid	1	0.02% w/v	OctreoScan® (Mallinckrodt) 0.02% w/v
Gentisic acid ethanolamine	1	2%	M.V.I. 12® (Astra) 2%
Glutamate monosodium	2	0.1% w/v	Varivax® (Merck) 0.1% w/v
Formaldehyde sulfoxylate sodium	9	0.02–0.5% w/v	Terramycin solution (Pfizer) 0.5% w/v
Metabisulfite potassium	1	0.10%	Vasoxyl® (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	32	0.02–1% w/v	Intropin® (DuPont) 1% w/v
Monothioglycerol (Thioglycerol)	6	0.1–1%	Terramycin solution (Pfizer) 1%
Propyl gallate	2	0.02%	Navane® (Pfizer) 0.02%
Sulfite sodium	7	0.05–0.2% w/v	Enlon® (Ohmeda) 0.2% w/v
Tocopherol alpha	1	0.005% w/v	AmBisome® (Fujisawa) 0.005%
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine® (Forest) 0.66% w/v

ascorbic acid. Thus, they can be consumed during the shelf-life of the product.

3. *Antioxidant synergists*: These enhance the effect of antioxidants, e.g., EDTA.

Table 4 summarizes the antioxidants, their frequency of use, concentration range, and examples of products containing them. Sulfite, bisulfite, and metabisulfite constitute the majority of antioxidants used in parenteral products despite several reports of incompatibility and toxicity (27, 28). Butylated hydroxy anisole, butylated hydroxy toluene, alpha tocopherol, and propyl gallate are primarily used in semi/nonaqueous vehicles because of their low aqueous solubility (29). Ascorbic acid/sodium ascorbate may serve as an antioxidant, buffer and chelating agent in the same formulation. Some amino acids such as cysteine also function as effective antioxidants.

The Committee for Proprietary Medicinal Products (CPMP) guideline calls for a full explanation and justification for including antioxidants in the formulation (30). It further states that antioxidants should only be included in a formulation if it has been proven that their use cannot be avoided. Thus, it is imperative to first try inert gas (nitrogen or argon) in the headspace to prevent oxidation. If the antioxidant has to be included, its concentration must be justified in terms of efficacy and safety. Antioxidants such as sulfites and metabisulfites are especially undesirable.

Some antioxidants possess antimicrobial properties, such as propyl gallate and butylated hydroxy anisole, which are somewhat effective against bacteria. Butylated hydroxy toluene has demonstrated some antiviral activity. Compatibility of antioxidants with the drug, packaging system and the body should be studied carefully. For example, tocopherols may be absorbed onto plastics; ascorbic acid is incompatible with alkalis, heavy metals, and oxidizing materials such as phenylephrine, and sodium nitrite; and propyl gallate forms complexes with metal ions such as sodium, potassium and iron.

Preservatives

Benzyl alcohol is the most common antimicrobial preservative present in parenteral formulations (Table 5). This observation is consistent with other surveys (6, 31). Parabens are the second most common preservatives. Surprisingly, thimerosal is also common, especially in vaccines, even though some individuals are sensitive to mercurics. Several preservatives can volatilize easily (such as benzyl alcohol, and phenol) and, therefore, should not be used for lyophilized dosage form. Chlorocresol is purported to be a good preservative for parenterals, but our survey did not find any examples of commercial products containing chlorocresol. The British Pharmaceutical Codex and Martindale list chlorocresol as a preservative to be used in multidose aqueous injections at concentrations of 0.1% but no examples of injectable products have been provided (32, 33).

Antimicrobial preservatives are allowed in multidose injections to prevent growth of microorganisms that may accidentally enter the container during withdrawal of the dose. However, they are discouraged from being used in single-dose injections in the United States while the EP and BP allow aqueous preparations, that are manufactured using aseptic techniques, to contain suitable preservatives. It should be emphasized that preservatives should never be used as a substitute for inadequate good manufacturing practices (GMP). BP and EP prohibit antimicrobials from single-dose

Table 5 Antimicrobial preservatives

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan® (Schering) 0.02% w/v
Benzethonium chloride	4	0.01%	Benadryl® (Parke-Davis) 0.01% w/v
Benzyl alcohol	85	0.75–10%	Progesterone (United Res) 10%
Chlorbutanol	18	0.25–0.5%	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	5	0.1–0.35%	Humalog® (Lilly) 0.35%
Myristyl gamma–picolinium chloride	2	0.0195–0.169% w/v	Depo-Provera® (Pharmacia-Upjohn) 0.169% w/v
Paraben methyl	52	0.05–0.18%	Inapsine® (Janssen) 0.18% w/v
Paraben propyl	44	0.01–0.1%	Xylocaine w/ Epinephrine (Astra) 0.1% w/v
Phenol	50	0.2–0.5%	Calcimar® (Rhone-Poulanc) 0.5% w/v
2-Phenoxyethanol	4	0.50%	Havrix® (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	3	0.001%	Antivenin® (Wyeth-Ayerst) 0.001%
Thimerosal	48	0.003–0.012%	Atgam® (Pharmacia-Upjohn) 0.01%

Table 6 Maximum permissible amount of preservatives and antioxidants

Excipient	Maximum limit in USP
Mercurial compounds	0.01%
Cationic surfactants	0.01%
Chlorobutanol	0.50%
Cresol	0.50%
Phenol	0.50%
Sulfur dioxide or an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium	0.20%

injections where the dose volume is greater than 15 mL or if the drug product is to be injected via intracisternal, or any route which gives access to the cerebrospinal fluid (CSF). Toxicity is the primary reason for minimizing the use of antimicrobial preservatives. For example, many individuals are allergic to mercury preservatives while benzyl alcohol is contraindicated in children under the age of 2. USP has also placed some restrictions on the maximum concentration of preservatives allowed in the formulation to address toxicity and allergic reactions (Table 6). The World Health Organization (WHO) has set an estimated total acceptable daily intake for sorbate (as acid, calcium, potassium and sodium salts) as not more than 25 mg/kg body weight. The efficacy of the preservative should be assessed during product development using Antimicrobial Preservative Effectiveness Testing (PET) (34–36). Thus, an aqueous-preserved parenteral product can be used up to a maximum of 28 days after the container has been opened (37). Obviously, 28 days has to be justified by performing PET on the finished product in the final package. On the other hand, unpreserved products preferably should be used immediately following opening, reconstitution, or dilution.

Buffers

Buffers are added to a formulation to adjust the pH in order to optimize solubility and stability. For parenteral preparations, the pH of the product should be close to physiologic pH. The selection of buffer concentration (ionic strength) and buffer species is important. For example, 5–15 m*M* of citrate buffers are used in the formulation but increasing buffer concentration to >50 m*M* will result in excessive pain on subcutaneous injection and toxic effects due to the chelation of calcium in the blood.

Buffers have maximum buffer capacities near their pK_a. For products that may be subjected to excessive temperature fluctuations during processing (such as sterilization or lyophilization), it is important to select buffers with a small ΔpK_a/°C. Thus, Tris, whose ΔpK_a/°C is large (−0.028/°C), the pH of buffer made at 25°C will change from 7.1 to 5.0 at 100°C. This may dramatically alter the stability or solubility of the drug. Similarly, the best buffers for a lyophilized product may be those that show the least pH change upon cooling, that do not crystallize out, and that can remain in the amorphous state protecting the drug. For example, replacing succinate with glycolate buffer improves the stability of lyophilized interferon-γ (38). During the lyophilization of mannitol that contains succinate buffer at pH 5, monosodium succinate crystallizes, reducing the pH and resulting in the unfolding of interferon-γ. This pH shift is not seen with glycolate buffer.

Table 7 lists buffers and chemicals used to adjust the pH of formulations and the product pH range. Phosphate, citrate, and acetate are the most common buffers used in parenteral products. Mono- and diethanolamines are added to adjust pH and form corresponding salts. Hydrogen bromide, sulfuric acid, benzene sulfonic acid, and methane sulfonic acids are added to drugs which are salts of bromide (Scopolamine HBr, Hyoscine HBr), sulfate (Nebcin, Tobramycin sulfate), besylate (Tracrium Injection, Atracurium besylate) or mesylate (DHE 45 Injection, Dihydroergotamine mesylate). Glucono delta lactone is used to adjust the pH of Quinidine gluconate. Benzoate buffer, at a concentration of 5%, is used in Valium Injection. Citrates are a common buffer that can have a dual role as chelating agents. The amino acids lysine and glycine, function as buffers and stabilize proteins and peptide formulations. These amino acids are also used as lyo-additives and may prevent cold denaturation. Lactate and tartrate are occasionally used as buffer systems. Acetates are good buffers at low pH, but they are not generally used for lyophilization because of potential sublimation of acetates.

Bulking Agents, Protectants, and Tonicity Adjusters

Table 8 lists additives that are used to modify osmolality, and as bulking or lyo/cryoprotective agents. Dextrose and sodium chloride are used to adjust tonicity in the majority of formulations. Some amino acids such as glycine, alanine, histidine, imidazole, arginine, asparagine, and aspartic acid are used as bulking agents for lyophilization and also can serve as stabilizers, and/or as buffers.

Table 7 Buffers and pH-adjusting agents

Excipient	pH Range	Example
Acetate		
Sodium	3.7–4.3	Syntocinon® (Novartis)
Acetic acid	3.7–4.3	Syntocinon® (Novartis)
Glacial acetic acid	3.5–5.5	Brevibloc® (Ohmeda)
Ammonium	6.8–7.8	Bumex Injection® (Roche)
Ammonium sulfate	—	Innovar® (Astra)
Ammonium hydroxide	—	Triostat® (Jones Medical)
Arginine	7.0–7.4	Retavase® (Boehringer)
Aspartic acid	5.7–6.4	Pepcid® (Merck)
Benzene sulfonic acid	3.25–3.65	Nimbex® (Glaxo Wellcome)
Benzoate Sodium/acid	6.2–6.9	Valium® (Roche)
Bicarbonate	5.5–11.0	Cenolate® (Abbott)
Boric acid/sodium		Comvax® (Merck)
Carbonate, sodium	5.0–11.0	Hyperab® (Bayer)
Citrate		
Acid	3.0–5.5	DTIC-Dome® (Bayer)
Sodium	3.5–6.5	Amikin® (Bristol Myers)
Disodium	—	Cerezyme® (Genzyme)
Trisodium	—	Cerezyme® (Genzyme)
Diethanolamine	9.5–10.5	Bactim IV® (Roche)
Glucono delta lactone	5.5–7.0	Quinidine Gluconate(Lilly)
Glycine/glycine HCl	6.4–7.2	Hep-B Gammagee® (Merck)
Histidine/histidine HCl	6.5	Doxil® (Sequus)
Hydrochloric acid	6.0–7.6	Amicar® (Immunex)
Hydrobromic acid	3.5–6.5	Scopolamine (UDL)
Lactate sodium/Acid	2.7–5.7	Innovar® (Janssen)
Lysine (L)	—	Eminase® (Roberts)
Maleic acid	3.0–5.0	Librium® (Roche)
Meglumine	6.5–8.0	Magnevist® (Berlex)
Methanesulfonic acid	3.2–4.0	DHE-45® (Novartis)
Monoethanolamine	8.0–9.0	Terramycin (Pfizer)
Phosphate		
Acid	6.5–8.5	Saizen® (Serono Labs)
Monobasic potassium	6.7–7.3	Zantac® (Glaxo-Wellcome)
Monobasic sodium[a]	6.0–8.0	Pregnyl® (Organon)
Dibasic sodium[b]	6.7–7.8	Zantac® (Glaxo-Wellcome)
Tribasic sodium	—	Synthroid® (Knoll)
Sodium hydroxide	Broad range	Optiray® (Mallinckrodt)
Succinate sodium/Disodium	5.0–6.0	AmBisome® (Fujisawa)
Sulfuric acid	3.0–6.5	Nebcin® (Lilly)
Tartrate sodium/acid	2.7–6.2	Methergine® (Novartis)
Tromethamine	6.0–7.5	Optiray® (Mallinckrodt)

[a]Sodium biphosphate, sodium dihydrogen phosphate, or Na dihydrogen orthophosphate.
[b]Sodium phosphate, disodium hydrogen phosphate.

Monosaccharides (dextrose, glucose, maltose, lactose), disaccharides (sucrose, trehalose), polyhydric alcohols (inositol, mannitol, sorbitol), glycols (PEG 3350), Povidone (polyvinylpyrrolidone, PVP) and proteins (albumin, gelatin) are commonly used as lyo-additives. Hydroxyethyl starch (hetastarch) and pentastarch, which are currently used as plasma expanders in commercial injectable products such as Hespan and Pentaspan, also are being evaluated as protectants during freeze-drying of proteins.

Table 8 Bulking agents, protectants, and tonicity adjusters

Excipient	Example
Alanine	Thrombate III® (Bayer)
Albumin	Bioclate® (Arco)
Albumin (human)	Botox® (Allergan)
Amino acids	Havrix® (Smith Kline Beecham)
Arginine (L)	Activase® (Genentech)
Asparagine	Tice BCG® (Organon)
Aspartic acid (L)	Pepcid® (Merck)
Calcium chloride	Phenergan® (Wyeth-Ayerst)
Cyclodextrin-alpha	Edex® (Schwartz)
Cyclodextrin-gamma	Cardiotec® (Squibb)
Dextran 40	Etopophos® (Bristol Myers)
Dextrose	Betaseron® (Berlex)
Gelatin (cross-linked)	Kabikinase® (Pharmacia-Upjohn)
Gelatin (hydrolyzed)	Acthar® (Rhone-Poulanc Rorer)
Lactic & glycolic acid copolymers	Lupron Depot® (TAP)
Glucose	Iveegam® (Immuno-US)
Glycerine	Tice BCG® (Organon)
Glycine	Atgam® (Pharmacia-Upjohn)
Histidine	Antihemophilic Factor, human (Am. Red Cross)
Imidazole	Helixate® (Armour)
Inositol	OctreoScan® (Mallinckrodt)
Lactose	Caverject® (Pharmacia-Upjohn)
Magnesium chloride	Terramycin Solution (Pfizer)
Magnesium sulfate	Tice BCG® (Organon)
Maltose	Gamimune N® (Bayer)
Mannitol	Elspar® (Merck)
Polyethylene glycol 3350	Bioclate® (Arco)
Polylactic acid	Lupron Depot® (TAP)
Polysorbate 80	Helixate® (Armour)
Potassium chloride	Varivax® (Merck)
Povidone	Alkeran® (Glaxo-Wellcome)
Sodium chloride	WinRho SD® (Univax)
Sodium cholesteryl sulfate	Amphotec® (Sequus)
Sodium succinate	Actimmune® (Genentech)
Sodium sulfate	Depo-Provera® (Pharmacia-Upjohn)
Sorbitol	Panhematin® (Abbott)
Sucrose	Prolastin® (Bayer)
Trehalose (alpha, alpha)	Herceptin® (Genentech)

PVP has been used in injectable products as a solubilizing agent, a protectant and as a bulking agent. Only pyrogen-free grade, with low molecular weight (*K* value less than 18) should be used in parenteral products to allow for rapid renal elimination. PVP not only solubilizes drugs such as rifampicin, but it also can reduce the local toxicity as seen in oxytetracycline injection.

Many proteins can be stabilized in the lyophilized state if the stabilizer and protein do not phase separate during freezing or the stabilizer does not crystallize out. In the case of Neupogen® (GCSF), the original formulation was modified by replacing mannitol with sorbitol to prevent the loss of activity of liquid formulation in case of accidental freezing (24). Mannitol crystallizes if the solution freezes while sorbitol remains in an amorphous state protecting GCSF. Similarly, it is useful that the drug remains dispersed in the stabilizer upon freezing of the solution. Thus, Cefoxitin, a cephalosporin, is more stable when freeze-dried with sucrose than with trehalose, although the glass transition temperature and structural relaxation time is much

greater for trehalose than sucrose (39). FTIR data indicated that the trehalose–cefoxitin system phase separated into two nearly pure components, resulting in no protection (stability). Similarly, dextran was not found to be as useful a cryoprotectant for protein as sucrose because dextran and protein underwent phase segregation as the solution started to freeze. The mechanism of cryoprotection in the solution has been explained by the preferential exclusion hypothesis (40).

Trehalose is a nonreducing disaccharide composed of two D-glucose monomers. It is found in several animals that can withstand dehydration and therefore was suggested as a stabilizer of drugs that undergo denaturation during spray or freeze-drying (41). Herceptin® (Trastuzumab) is a recombinant DNA-derived monoclonal antibody (MAb) that is used for treating metastatic breast cancer. The MAb has been stabilized in the lyophilized formulation using α,α-trehalose dihydrate. Trehalose has also been used as a cryoprotectant to prevent liposomal aggregation and leakage. In the dried state, carbohydrates such as trehalose, and inositol, exert their protective effect by acting as a water substitute (42).

Additives may have to be included in the formulation to adjust the specific gravity. This is important for drugs that upon administration may come in contact with CSF. CSF has a specific gravity of 1.0059 at 37°C. Solutions that have the same specific gravity as that of CSF are termed isobaric, while those solutions that have specific gravity greater than that of CSF are called hyperbaric. Upon administration of a hyperbaric solution in the spinal cord, the injected solution will settle and will affect spinal nerves at the end of the spinal cord. For example, Dibucaine hydrochloride solution (Nupercaine® 1:200) is isobaric, while Nupercaine 1:500 is hypobaric (specific gravity of 1.0036 at 37°C). Nupercaine heavy solution is made hyperbaric by addition of 5% dextrose solution, and this solution will block (anesthetize) the lower spinal nerves as it settles in the spinal cord.

Special Additives

Special additives serve special functions in pharmaceutical formulations (Table 9). The following is a summary of special additives along with their intended use:

1. Calcium gluconate injection (American Regent) is a saturated solution of 10% w/v. Calcium D-saccharate tetrahydrate 0.46% w/v is added to prevent crystallization during temperature fluctuations.
2. Cipro IV® (Ciprofloxacin, Bayer) contains lactic acid as a solubilizing agent for the antibiotic.
3. Premarin Injection® (Conjugated Estrogens, Wyeth-Ayerst Labs) is a lyophilized product that contains simethicone to prevent the formation of foam during reconstitution.
4. Dexamethasone acetate (Dalalone DP, Forest, Decadron-LA, Merck) and Dexamethasone sodium phosphate (Merck) are available as a suspension or a solution. These dexamethasone formulations contain creatine or creatinine as additives.
5. Adriamycin RDF® (Doxorubicin hydrochloride, Pharmacia-Upjohn) contains methyl paraben, 0.2 mg/mL to increase dissolution (43).
6. Ergotrate maleate (Ergonovine maleate, Lilly) contains 0.1% ethyl lactate as a solubilizing agent.
7. Estradurin Injection® (Polyestradiol phosphate, Wyeth-Ayerst Labs) uses Niacinamide (12.5 mg/ml) as a solubilizing agent. Hydeltrasol® also contains niacinamide. The concept of hydrotropic agents to increase water solubility has been tried on several compounds, including proteins (44, 45).
8. Aluminum, in the form of aluminum hydroxide, aluminum phosphate or aluminum potassium sulfate, is used as adjuvant in various vaccine formulations to elicit an increased immunogenic response.
9. Lupron Depot Injection® is lyophilized microspheres of gelatin and glycolic–lactic acid for intramuscular (IM) injection. Nutropin Depot consists of poly-lactate–glycolate microspheres.
10. Gamma cyclodextrin is used as a stabilizer in Cardiotec® at a concentration of 50 mg/mL.
11. Alprostadil (Edex®, Schwartz) is a lyophilized product of Prostaglandin E_1 in α-cyclodextrin inclusion complex. The complex has better stability and aqueous solubility than the drug itself.
12. Itraconazole (Sporanox®, Janssen) is solubilized as a molecular inclusion complex using hydroxypropyl-β-cyclodextrin.
13. Sodium caprylate (sodium octoate) has antifungal properties, but it is also used to improve the stability of albumin solution against the effects of heat. Albumin solution can be pasteurized by heating at 60°C for 10 h in the presence of sodium caprylate. Acetyl tryptophanate sodium is also added to albumin formulations.
14. Meglumine (*N*-methylglucamine) is used to form in situ salt. For example, diatrizoic acid, an X-ray contrast agent, is more stable when autoclaved as meglumine salt than as sodium salt (46). Meglumine is also added to Magnevist®, a magnetic resonance contrast agent.
15. Tri-*n*-butyl phosphate is present as an excipient in human immune globulin solution (Venoglobulin®). Its exact function in the formulation is not known, but it may serve as a scavenging agent.

Table 9 Special additives

Excipient	Example
Acetyl tryptophanate	Human Albumin (American Red Cross)
Aluminum hydroxide	Recombivax HB® (Merck)
Aluminum phosphate	Tetanus Toxoid Adsorbed (Wyeth-Ayerst)
Aluminum potassium sulfate	TD Adsorbed Adult (Pasteur Merieux)
ε-Aminocaproic acid	Eminase® (Roberts)
Calcium D-saccharate	Calcium Gluconate (American Regent)
Caprylate sodium	Human Albumin (American Red Cross)
8-Chlorotheophylline	Dimenhydrinate® (Steris)
Creatine	Dalalone DP® (Forest)
Creatinine	Decadron® (Merck)
Cholesterol	Doxil® (Sequus)
Cholesteryl sulfate sodium	Amphotec® (Sequus)
Alpha-cyclodextrin	Edex® (Schwartz)
Gamma-cyclodextrin	Cardiotec® (Squibb)
Hydroxypropyl beta cyclodextrin	Sporanox® (Janssen)
Distearyl Phosphatidylcholine	DaunoXome® (Nexstar)
Distearyl Phosphatidylglycerol	MiKasome® (NeXstar)
L-Alpha-Dimyristoylphosphatidylcholine	Abelcet® (The Liposome Co.)
L-Alpha-Dimyristoylphosphatidylglycerol	Abelcet® (The Liposome Co.)
Dioleoylphosphatidylcholine (DOPC)	DepoCyt® (Chiron)
Dipalmitoylphosphatidylglycerol (DPPG)	DepoCyt® (Chiron)
MPEG-distearoyl phosphoethanolamine	Doxil® (Sequus)
Diatrizoic acid	Conray® (Mallinckrodt)
Ethyl lactate	Ergotratc maleate (Lilly)
Ethylenediamine	Aminophylline (Abbott)
L-Glutamate sodium	Kabikinase® (Pharmacia-Upjohn)
Hydrogenated soy phosphatidylcholine	Doxil® (Sequus)
Iron ammonium citrate	Tice BCG® (Organon)
Lactic acid	Cipro IV® (Bayer)
D,L-Lactic and glycolic acid copolymer	Zoladex® (Zeneca)
Meglumine	Magnevist® (Berlex)
Niacinamide	Estradurin® (Wyeth-Ayerst)
Paraben methyl	Adriamycin RDF® (Pharmacia-Upjohn)
Protamine	Insulatard NPH® (Novo Nordisk)
Simethicone	Premarin Injection® (Wyeth-Ayerst)
Saccharin sodium	Compazine Injection® (Smith Kline Beecham)
Tri-*n*-butyl phosphate	Venoglobulin® (Alpha Therapeutic)
Triolein	DepoCyt® (Chiron)
von Willebrand factor	Bioclate® (Arco)
Zinc	Lente Insulin® (Novo Nordisk)
Zinc acetate	Nutropin Depot® (Genentech)
Zinc carbonate	Nutropin Depot® (Genentech)
Zinc oxide	Humalog® (Lilly)

16. von Willebrand factor is used to stabilize recombinant antihemophilic factor (Bioclate®).
17. Maltose serves as a tonicity adjuster and stabilizer in immune globulin formulation (Gamimune N®).
18. Epsilon amino caproic acid (6-amino hexanoic acid) is used as a stabilizer in anistreplase (Eminase Injection®).
19. Zinc and protamine have been added to insulin to form complexes and control the duration of action.

The FDA has published the "Inactive Ingredient Guide" which lists all excipients in alphabetical order (14). Each ingredient is followed by the route of administration, and

Table 10 List of excipients from the 1996 FDA Inactive Ingredient Guide

Benzyl chloride	Poloxamer 165
Butyl paraben	PEG 4000
Caldiamide sodium	Polyoxyethylene fatty acid esters
Calteridol calcium	Polyoxyethylene sorbitan monostearate
Cellulose (microcrystalline)	Polyoxyl 35 castor oil
Deoxycholic acid	Polysorbate 40
Dicyclohexyl carbodiimide	Polysorbate 85
Diethyl amine	Potassium hydroxide
Disofenin	Potassium phosphate, dibasic
Docusate sodium	Sodium bisulfate
Edamine	Sodium chlorate
Exametazime	Sodium hypochloride
Gluceptate sodium	Sodium iodide
Gluceptate calcium	Sodium pyrophosphate
Glucuronic acid	Sodium thiosulfate, anhydrous
Guanidine HCl	Sodium trimetaphosphate
Iofetamine HCl	Sorbitan monopalmitate
Lactobionic acid	Stannous chloride
Lidofenin	Stannous fluoride
Medrofenin	Stannous tartrate
Medronate disodium	Starch
Medronic acid	Succimer
Methyl boronic acid	Succinic acid
Methyl cellulose	Sulfurous acid
Methylene blue	Tetrakis (1-isocyano-2-methoxy-2-methyl-propionate) copper (I) Tc
N-(Carbamoyl-methoxy polyethylene glycol 2000)-1,2- distearoyl	Thiazoximic acid
N-2-Hydroxyethyl piperazine *N*′-2′ ethane sulonic acid	Urea
Nioxime	Zic acetate
Nitric acid	Zinc chloride
Oxyquinoline	2-ethyl hexanoic acid
Pentate (DTPA) calcium trisodium	PEG vegetable oil

in some cases, the range of concentration used in the approved drug product. However, this list does not provide the name of commercial product(s) corresponding to each excipient. Table 10 summarizes all the excipients included in the "Inactive Ingredient Guide" that do not appear in the Physician's Desk Reference (PDR), GenRx, or Handbook of Injectable Drugs.

Similarly, in Japan the "Japanese Pharmaceutical Excipients Directory" is published by the Japanese Pharmaceutical Excipients Council, with the cooperation and guidance of the Ministry of Health and Welfare (47). This directory divides the excipients into:

1. *Official*. Those 590 excipients that have been recognized in the JP, Japanese Pharmaceutical Codex, and Japanese Pharmaceutical Excipients, and for which testing methods and standards have been determined. Table 11 summarizes official excipients used in parenteral products.
2. *Nonofficial Excipients*. These 522 excipients are used in pharmaceutical products sold in Japan and will be included in the official book or in supplemental editions. The nonofficial excipients, used in parenteral products, are listed in Table 12.

REGULATORY PERSPECTIVE

The International Pharmaceutical Excipients Council (IPEC) has classified excipients into the following four classes, based on available safety testing information (48):

Table 11 Official Japanse pharmceutical excipients

Name	Uses	Administration route
Acacia	Diluent, dispersing agent	im
Acetic acid	Buffer agent, solvent, stabilizer	iv, im, sc
L-Alanine	Stabilizer	iv, im,
Aluminum monostearate	Dispersing agent, stabilizer, vehicle	other inj.
Aluminum potassium sulfate	pH adjustment, stabilizer	im, sc
Aminoacetic acid	Buffering agent, solubilizer, stabilizer, suspending agent, vehicle	iv, im, sc, ic
Anhydrous citric acid	Buffer agent, pH adjustment, solubilizing agent, stabilizer	iv, im, other inj.
Anhydrous disodium hydrogen phosphate	Buffering agent, pH adjustment, solubilizer, stabilizer, suspending agent	iv, im, sc, other inj.
Anhydrous sodium dihydrogen phosphate	Buffering agent, pH adjustment, stabilizer	iv, im, other inj.
Arginine hydrochloride	Buffering agent, solubilizing agent, stabilizer	iv, im, sc
Ascorbic acid	Antioxidant, buffering agent, Stabilizer	iv, im, sc, ia
L-Aspartic acid	Solubilizer, stabilizer, vehicle	iv, im
Benzylkonium chloride	Buffering agent, preservative, stabilizer	
Benzethonium chloride	Dispersing agent, preservative, stabilizer	iv, im, other inj.
Benzoic acid	Buffering agent, preservative, stabilizer	iv, im
Benzyl alcohol	Preservative, solubilizer, solvent, stabilizer	iv, im, sc, ic, other inj.
Benzyl benzoate	Antiseptic, solubilizer, solvent	im
Calcium bromide	Isotonicity, stabilizer	iv
Calcium chloride	Isotonicity, suspending agent	iv
Calcium disodium edetate	Stabilizer	iv, ic, ia, is, other inj
Calcium gluconate	Buffering agent, stabilizer	iv, im, sc
Calcium oxide	Solubilizing agent	iv
Calcium D-saccharate	Stabilizer	iv
Camellia oil	Solvent	im, sc
Carmellose sodium	Emulsifying agent, solubilizing agent, stabilizer, suspending agent	im, ic, sc, other inj.
Castor oil	Solubilizer, solvent	im
Chlorobutanol	Buffering agent, preservative	iv, im, sc
Citric acid	Antioxidant, buffering agent, pH adjustment, preservative, solubilizing agent, stabilizer	iv, im, sc, ia,
Concentrated glycerin	Isotonicity, solubilizer, stabilizer	iv, im, sc
Creatinine	Buffering agent, stabilizer	iv, im, ic, sc, other inj.
Cresol	Preservative	iv, im, sc
L-Cystine	Stabilizer	iv
Dehydrated ethanol	Solubilizer, solubilizing agent, solvent	iv, im, sc
Dextran 40	Stabilizer, vehicle	iv, im
Dextran 70	Stabilizer	sc
Dibasic potassium sulfate	Buffering agent, pH adjustment	iv, im, sc
Dibasic sodium citrate	Buffering agent, vehicle	iv
Dibasic sodium phosphate	Buffering agent, pH adjustment, solubilizing agent, stabilizer, vehicle	iv, im, sc, ia, is, ic, other inj.
Dilute hydrochloric acid	Buffering agent, pH adjustment, solubilizer, stabilizer	iv, im, sc
N, *N*-Dimethylacetamide	Solvent	iv

(*Continued*)

Table 11 Official Japanse pharmceutical excipients (*Continued*)

Name	Uses	Administration route
Glucose	Buffering agent, isotonicity, solubilizer, stabilizer, vehicle	iv, im, sc, ic
Glycerin	Dispersing agent, isotonicity, preservative, solubilizing agent, solvent, stabilizer, suspending agent, vehicle	iv, im, sc, other inj.
Heparin sodium	Stabilizer	iv
L-Histidine	Stabilizer	iv
Hydrochloric acid	pH adjustment, solubilizing agent, stabilizer	iv, im, sc, ia, is,ic, other inj.
N-Hydroxyethyl lactamide solution	Solubilizing agent	iv
Hydroxypropylcellulose	Emulsifying agent, solubilizer, stabilizer, suspending agent, vehicle	im
Isotonic sodium chloride solution	Isotonicity, solvent	iv, im, sc, ia, ic, other inj.
Lactic acid	Buffering agent, pH adjustment, solubilizer, stabilizer,	iv, im, sc
Lactose	Dispersing agent, suspending agent, vehicle	iv, im, sc, ia, ic, other inj.
Lidocaine	Solubilizing agent, solvent	iv, im
L-Lysine-L-Glutamate	Solubilizing agent, stabilizer	iv
Lysine hydrochloride	Stabilizer	iv
Macrogol 400 (PEG 400)	Solubilizing agent	iv
Macrogol 4000 (PEG 4000)	Isotonicity, solubilizer, solvent, stabilizer, suspending agent, vehicle, wetting agent	iv, im, sc
Magnesium chloride	Isotonicity, solubilizing agent, stabilizer	iv
Magnesium gluconate	Stabilizer	iv
Magnesium sulfate	Stabilizer	iv, im, sc
Maleic acid	Buffering agent, pH adjustment, stabilizer	im
Maleic anhydride	Solubilizer, stabilizer	iv
Maltose	Stabilizer	iv, im, sc, ic, other inj.
D-Mannitol	Isotonicity, solubilizing agent, stabilizer	iv, im, sc, ic, other inj.
Meglumine	pH adjustment, solubilizing agent	iv
Meprylcaine hydrochloride	Soothing agent	iv, im, sc
Methanesulfonic acid	pH adjustment	im, sc
L-Methionine	Stabilizer	dental inj.
Methyl parahydroxybenzoate	Preservative, stabilizer	iv, im, sc, ic, other inj.
Monobasic potassium phosphate	Buffer agent, isotonocity, pH adjustment, solubilizing agent, stabilizer	iv, im, sc, ic
Monoethanolamine	Buffer agent, pH adjustment, solubilizer, stabilizer	iv
MonopotassiumL-Glutamate monohydrate	Preservative, stabilizer	sc
Monosodium L-Glutamate monohydrate	Buffer agent	iv, im, sc
Nicotinamide	Isotonicity, solubilizing agent, stabilizer	iv, im, sc, other inj.
Peanut oil	Solubilizer, solvent, suspending agent, vehicle	im
Peptone, caesin	Stabilizer	sc
Phenol	Antiseptic, preservative	ic, im, sc, ic, othe inj.

(*Continued*)

Table 11 Official Japanse pharmceutical excipients (*Continued*)

Name	Uses	Administration route
Disodium edetate	Antioxidant, antiseptic, preservative, stabilizer	iv, ia, other inj.
Phosphoric acid	Buffer agent, isotonicity, pH adjustment, solubilizing agent, stabilizer	iv, im, sc
Polyoxyethylene hydrogenated castor oil 60	Dispersing agent, emulsifying agent, solubilizing agent, stabilizer, surfactant, suspending agent, vehicle	iv, im, sc
Polyoxyethylene hydrogenated castor oil 51	Dispersing agent, emulsifying agent, solubilizing agent	iv, im, sc, is
Polyoxyethylene [160] Polyoxypropylene [30] glycol	Dispersing agent, emulsifying agent, solubilizer, stabilizer, suspending agent, vehicle, surfactant, wetting agent	iv
Polysorbate 80	Dispersing agent, emulsifying agent, solubilizer, surfactant, stabilizer, suspending agent, vehicle, wetting agent	iv, im, sc, ic, other inj.
Potassium sulfate	Stabilizer	local anesthetic inj.
Powdered acacia	Dispersing agent, suspending agent	im, sc
Propylene glycol	Dispersing agent, isotonicity, preservative, solubilizer, solvent, stabilizer, suspending agent, vehicle, wetting agent	iv, im, sc
Propyl parahydroxybenzoate	Antiseptic, preservative, stabilizer	iv, im, sc, ic, other inj
Protamine sulfate	Prolongating agent	sc
Purified gelatin	Base, stabilizer, suspending agent, vehicle	iv, im, sc
Purified soybean lecithin	Dispersing agent, emulsifying agent, solubilizer, stabilizer	iv
Purified yolk lecithin	Emulsifying agent	iv
Sesame oil	Base, solubilizing agent, solvent, stabilizer, vehicle	iv, im, sc, other inj.
Sodium acetate	Buffer agent, pH adjustment, solubilizing agent, stabilizer	iv, im, sc, other inj.
Sodium acetyl tryptophan	Stabilizer	iv, sc
Sodium benzoate	Antiseptic, buffer agent, preservative, solubilizer, stabilizer	im
Sodium bicarbonate	Buffer agent, isotonicity, pH adjustment, solubilizer, stabilizer	iv, im, sc, is, ic, other inj.
Sodium bisulfite	Antioxidant, isotonicity, stabilizer	iv, im, sc, other inj.
Sodium bromide	Isotonicity	iv, im, sc
Sodium caprylate	Stabilizer	iv, sc
Sodium carbonate	Buffer agent, pH adjustment, solubilizing agent, stabilizer	iv, im, sc
Sodium chloride	Base, buffering agent, isotonicity, solubilizer, stabilizer, suspending agent, vehicle	iv, im, sc, ia, is
Sodium chondroitin sulfate	Stabilizer	iv
Sodium citrate	Antiseptic, buffer agent, isotonicity, pH adjustment, solubilizer, stabilizer	iv, im, sc, ic, ia, is, other inj.
Sodium desoxycholate	Solubilizing agent	ic, iv, is
Sodium dihydrogen phosphate dihydrate	Buffer agent, isotonicity, pH adjustment, stabilizer	iv, im, sc, ia, is, other inj.
Sodium formaldehydesulfoxylate	Stabilizer, isotonicity, pH adjustment	iv, im
Sodium hydroxide	Solubilizer	iv, im, sc, ia, ic, other inj.

(*Continued*)

Table 11 Official Japanse pharmceutical excipients (*Continued*)

Name	Uses	Administration route
Sodium salicylate	Antiseptic, preservative, solubilizing agent, stabilizer	iv, im, sc
Sodium thiomalate	Antioxidant, stabilizer	im
Sodium thiosulfate	Solubilizer, stabilizer	iv, im, sc
Sorbitan sesquioleate	Base, emulsifying agent, solubilizing agent, stabilizer, surfactant, vehicle	iv, im
D-Sorbitol	Dispersing agent, isotonicity, plasiticizer, preservative, solubilizing agent, stabilizer	iv, im, sc, other inj.
D-Sorbitol solution	Base, isotonicity, solubilizing agent, stabilizer, vehicle	im, sc, other inj
Soybean oil	Base, solubilizer, solvent, vehicle	iv
Stannous chloride	Reducing agent	iv
Sucrose	Base, stabilizer, vehicle	iv, sc
Tartaric acid	Buffering agent, pH adjustment, solubilizing agent, stabilizer, vehicle	iv, im
Thimerosal	Preservative	iv, im, sc
Thioglycolic acid	Solubilizing agent, stabilizer	iv, im, sc
Tribasic sodium phosphate	Buffering agent, pH adjustment	iv, im, sc
Trometamol (Tromethamine)	Buffering agent, solubilizing agent, stabilizer	iv, im, sc, ia, is, ic
Urea	Solubilizing agent, stabilizer, wetting agent	iv, im, sc
Water for injection	Solubilizer, solvent	iv, im, sc, ia, is, ic, other inj.
Xylitol	Isotonicity, stabilizer, vehicle	iv, im, other inj.
Zinc acetate	Stabilizer	sc
Zinc chloride	Stabilizer	im, sc
Zinc oxide	Dispersing agent, stabilizer, vehicle	sc

1. *New chemical excipients*: Require a full safety evaluation program. The estimated cost of safety studies for a new chemical excipient is approximately $35 million over 4–5 years. European Union (EU) directive 75/318/EEC states that new chemical excipients will be treated in the same way as new actives. In the United States a new excipient requires a Drug Master File (DMF) to be filed with the FDA. Similarly, in Europe a dossier needs to be established. Both the DMF and dossier contain relevant safety information. The IPEC Europe has issued a draft guideline (Compilation of Excipient Masterfiles Guidelines) which provides guidance to excipient producers on how to construct a dossier that will support a Marketing Authorization Application (MAA) while maintaining the confidentiality of the data.
2. *Existing chemical excipient—first use in man:* Implies that animal safety data exist since data may have been used in some other application. Additional safety information may have to be gathered to justify its use in humans.
3. *Existing chemical excipient*: Indicates that it has been used in humans but change in route of administration (say from oral to parenteral), new dosage form, higher dose, etc. may require additional safety information.
4. *New modifications or combinations of existing excipients:* A physical interaction NOT a chemical reaction. No safety evaluation is necessary in this case.

Simply because an excipient is listed as Generally Recognized As Safe (GRAS) does not mean that it can be used in parenteral dosage form. The GRAS list may include materials that have been proven safe for food (oral administration) but have not been deemed safe for use in an injectable product. This makes it difficult for the formulation development scientist to choose additives during the dosage form development.

Many pharmacopeial monographs for identical excipients differ considerably with regards to specifications, test criteria, and analytical methods. Thus, if a pharmaceutical manufacturer is going to supply a product

Table 12 Non-official Japanese pharmaceutical excipients

Excipients	Uses	Administration
Aluminum chloride	Potentiating agent	im, sc
Aluminum hydroxide	Adsorbent	sc, im
Aminoethyl sulfonic acid	Buffer, isotonicity, stabilizer, vehicle	iv, im
Ammonium acetate	pH adjusting agent	im
Anhydrous stannous chloride	Reducing agent	iv
L-Arginine	Buffer, stabilizer, solubilizer	iv, im, sc
Asepsis sodium bicarbonate	Stabilizer	iv
Butylhydroxyanisol	Antioxidant, stabilizer	iv
m-Cresol	Preservative	iv, im, sc, ic
L-Cysteine	Stabilizer	iv
Cysteine hydrochloride	Antioxidant, stabilizer	iv, im
Dichlorodifluoromethane	Propellant	iv
Diethanolamine	Buffer, solubilizer, stabilizer	iv
Diethylenetriaminepentaacetic acid	Stabilizer	iv
Ferric chloride	Stabilizer	iv
Highly purified yolk lecithin	Emulsifier	iv
Human serum albumin	Preservative, stabilizer	iv, im, sc
Hydrolyzed gelatin	Stabilizer	sc
Inositol	Stabilizer, vehicle	iv, im
Lidocaine hydrochloride	Soothing agent	im
D,L-Methionine	Stabilizer	im, sc
Monobasic sodium phosphate	Buffer, isotonicity, adjust pH	iv, im, sc
Oleic acid	Dispersing agent, solvent	iv
Phenol red	Coloring agent	sc
Polyoxyethylene castor oil	Base, emulsifying agent, solubilizing agent, stabilizer	iv
Polyoxyethylene hydrogenated castor oil	Base, emulsifying agent, solubilizer, stabilizer, suspending agent, vehicle	iv
Polyoxyethylene sorbitan monolaurate	Emulsifying agent, solubilizing agent, surfactant	iv, im, sc
Potassium pyrosulfite	Stabilizer	iv, sc, im
Potassium thiocyanate	Stabilizer	iv
Purified soybean oil	Solubilizer	iv
Sodium acetate, anhydrous	Buffer, pH adjuster, solubilizing agent, stabilizer	im
Sodium carbonate, anhydrous	Buffer, solubilizing agent	iv, im, ic
Sodium dihydrogen phosphate monohydrate	Buffering agent	ic
Sodium gluconate	Stabilizer, vehicle	iv, im
Sodium pyrophosphate, anhydrous	Dispersing agent, isotonicity, stabilizer	iv, im, is
Sodium sulfite	Antioxidant, stabilizer	iv
Sodium thioglycolate	Antioxidant, stabilizer	iv, im, sc
Sorbitan esters of fatty acids	Emulsifying agent, solubilizing agent, surfactant, stabilizer, suspending agent, vehicle	iv
Succinic acid	pH adjusting agent	iv
α-Thioglycerol	Antioxidant	iv, im, sc
Trienthanolamine	Buffer, pH adjuster, solubilizing agent, stabilizer	iv
Zinc chloride solution	Stabilizer	sc

throughout the world, the manufacturer will have to repeat testing on the same excipient several times in order to meet USP, JP, EP, BP, and other pharmacopoeias. EP, JP and USP are the main driving bodies within the International Conference on Harmonization (ICH) that are working on several of the commonly used excipients in order to

achieve a single monograph for each excipient. For example, benzyl alcohol undergoes degradation by a free radical mechanism to form benzaldehyde and hydrogen peroxide. The degradation products are much more toxic than the parent molecule. The *USP*, *JP*, and *EP* require three different chromatographic systems to test for organic impurity (mainly benzaldehyde). The harmonized monograph of benzyl alcohol will eliminate unnecessary repetition, which does not contribute to the overall quality of the product (49). The following 11 pharmacopoeial tests can be substituted by a single gas chromatography (GC) method:

EP:
- Benzaldehyde, related substance (GC)
- Halogenated compounds and halides (colorimetric test)
- Assay (hydroxyl value)

JP:
- Limit test for benzaldehyde
- Limit test for chlorinated compounds
- Distillation rangeAssay (hydroxyl value)

NF/USP:
- Benzaldehyde (HPLC)
- Halogenated compounds and halides (colorimetric test)
- Organic volatile impurities (GC)
- Assay (hydroxyl value)

The harmonization process is just beginning and is a major step in the right direction.

Another area where regulatory bodies are focusing their attention is the manufacturing process used to produce excipients. The IPEC has undertaken major initiatives to improve the quality of additives and has published "Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients" (50). The excipients may be manufactured for the food, cosmetic, chemical, agriculturo, or pharmaceutical industries, and the requirements for each area are different. The purpose of this guide is twofold: 1) to develop a quality system framework that can be used for suppliers of excipients and which will be acceptable to the pharmaceutical industry, and 2) to harmonize the requirements in the United States, Europe, and Japan.

The United States, Europe, and Japan require that all excipients be declared on the label if the product is an injectable preparation. The European guide for the label and package leaflet also lists excipients, that have special issues. These are addressed in an Annex (51). Table 13 contains a summary of some of these ingredients, which are commonly used as parenteral excipients and the corresponding safety information that should be included in the leaflet. Similarly, 21 CFR 201.22 requires prescription drugs containing sulfites to be labeled with a warning statement about possible hypersensitivity. An informational chapter in USP ⟨1091⟩ entitled "Labeling of Inactive Ingredients" provides guidelines for labeling of inactive ingredients present in dosage forms.

CRITERIA FOR THE SELECTION OF EXCIPIENT AND SUPPLIER

During the development of parenteral dosage forms, the formulator selects excipients that will provide a stable, efficacious, and functional product. The choice, and the characteristics of excipients should be appropriate for the intended purpose.

> An explanation should be provided with regard to the function of all constituents in the formulation, with justification for their inclusion. In some cases, experimental data may be necessary to justify such inclusion, e.g., preservatives. The choice of the quality of the excipient should be guided by its role in the formulation and by the proposed manufacturing process. In some cases, it may be necessary to address and justify the quality of certain excipients in the formulation (52).

Normally, a pharmaceutical development report is written in the United States, which should be available at the time of Pre-Approval Inspection (PAI). The development report contains the choice of excipients, their purpose and levels in the drug product, compatibility with other excipients, drug or package system, and how they may influence the stability and efficacy of the finished product.

The following key points should be considered in selecting an excipient and its supplier for parenteral products:

1. Influence of excipient on the overall quality, stability, and effectiveness of drug product.
2. Compatibility of excipient with drug and the packaging system.
3. Compatibility of excipient with the manufacturing process. For example, preservatives may be adsorbed by rubber tubes or filters, acetate buffers will be lost during lyophilization process, etc.
4. The amount or percentage of excipients that can be added to the drug product. Table 6 summarizes the maximum amount of preservatives and antioxidants allowed by various pharmacopoeias.

Table 13 Excipients for label and corresponding information for leaflet

Name	Information on leaflet
Arachis oil	Whenever arachis oil appears, peanut oil should appear beside it (because some individuals are sensitive to peanuts)
Benzoic acid and benzoates	It may increase the risk of jaundice in newborn babies
Benzyl alcohol	Contraindicated in infants or young children; up to 3 years old
Boric acid its salts and esters	Contraindicated in infants or young children; up to 3 years old
Dimethyl sulfoxide	Can cause stomach upset, diarrhea, drowsiness, and headache
Lactose	Unsuitable for people with lactose insufficiency, galactos emia, or glucose/galactose malabsorption syndrome
Organic mercury compounds	Can cause kidney damage
Parahydroxybenzoate and their esters	Known to cause urticaria. Generally delayed type reactions, such as contact dermatitis
Phenylalanine	Harmful for people with phenylketonuria
Polyethoxylated castor oils	Warning for parenterals only—hypersensitivity, drop in blood pressure, inadequate circulation, dyspnea, hot flushes
Potassium	For products administered iv—can cause pain at the site of injection or phlebitis
Sodium	May be harmful to people on low sodium diet
Sorbitol	Unsuitable in hereditary fructose intolerance
Sucrose (saccharose)	Unsuitable in hereditary fructose intolerance, glucose/galactose malabsorption syndrome, or sucrase-isomaltase deficiency
Sulphites (metabisulphites)	Can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptable people, especially those with a history of asthma or allergy
Urea	For products given iv—may cause venous thrombosis or phlebitis

5. Route of administration. The *USP*, *EP*, and *BP* do not allow preservatives to be present in injections intended to come in contact with brain tissues or CSF. Thus intracisternal, epidural, and intradural injections should be preservative free. Also, it is preferred that a drug product to be administered via intravenous (iv) route be free of particulate matter. However, if the size of the particle is well controlled, like in fat emulsion or colloidal albumin or amphotericin B dispersion, it can be administered by iv infusion.
6. Dose volume. All LVPs and those SVPs where the single dose injection volume can be greater than 15 ml are required by the EP/BP to be preservative free (unless justified). The USP recommends that special care be observed in the choice and the use of added substances in preparations for injections that are administered in volumes exceeding 5 ml.
7. Whether the product is intended for single or multiple dose use. According to USP, single dose injections should be free of preservative. The FDA takes the position that even though a single dose injection may have to be aseptically processed, the manufacturer should not use a preservative to prevent microbial growth. European agencies have taken a more lenient attitude on this subject.
8. The length or duration of time that the drug product will be used once the multidose injection is opened.
9. How safe is the excipient?
10. Does the parenteral excipient contain very low levels of lead, aluminum, or other heavy metals?
11. Does a dossier or DMF exist for the excipient?
12. Has the excipient been used in humans? Has it been used via a parenteral route and in the amount and concentration that is being planned?
13. Has the drug product that contains this excipient been approved throughout the world?
14. What is the cost of the excipient and is it readily available?
15. Is the excipient vendor following the IPEC GMP guide? Is the vendor ISO 9000 certified?
16. Will the excipient supplier certify the material to meet USP, BP, EP, JP, and other pharmacopoeias?
17. Has the supplier been audited by the FDA or the company's audit group? How did it fare?

Presence of impurities in excipients can have a dramatic influence on the safety, efficacy or stability of the drug product. Monomers or metal catalysts used during a polymerization process are toxic and can also destabilize the drug product if present in trace amounts. Due to safety

concerns, the limit of vinyl chloride (monomer) in polyvinyl pyrrolidone is nmt 10 ppm, and for hydrazine (a side product of polymerization reaction) nmt 1 ppm. Monomeric ethylene oxide is highly toxic and can be present in ethoxylated excipients such as PEGs, ethoxylated fatty acids, etc.

The FDA has issued a guidance suggesting that animal-derived materials such as egg yolk lecithin, and egg phospholipid) used in drug products, originating from Belgium, France, and the Netherlands between January and June 1999 should be investigated for the presence of dioxin and polychlorinated biphenyls. The contamination in the animal-derived product was probably due to contaminated animal feed.

Excipients manufactured by fermentation processes, such as dextrose, citric acid, mannitol, and trehalose, should be specially controlled for endotoxin levels. Mycotoxin (highly toxic metabolic products of certain fungi species) contamination of an excipient derived from natural material has not been specifically addressed by regulatory authorities. The German health authority issued a draft guideline in 1997 where a limit was specified for Aflotoxins M_1, B_1, and the sum of B_1, B_2, G_1, and G_2 in the starting material for pharmaceutical products.

Heavy metal contamination of excipients is a concern, especially for sugars, phosphate, and citrate. Several rules have been proposed or established. For example, the EP sets a limit of nmt 1 ppm of nickel in polyols. California Proposition 65 specifies a limit of nmt 0.5 μg of lead per day per product (53). Similarly, the FDA has proposed a guideline that would limit the aluminum content for all LVPs used in TPN therapy to 25 μg/L (54). Furthermore, it requires that the maximum level of aluminum in SVPs intended to be added to LVPs and pharmacy bulk packages, at expiration date, be stated on the immediate container label.

Physical and chemical stability of the excipient should be considered in assigning a reevaluation date. Since many drug products have a small amount of active and a comparatively high amount of excipients, degradation of even a small percentage of excipient can lead to levels of impurities sufficient to react or degrade a large percentage of active material. For example, benzyl alcohol decomposes via free radical mechanism in the presence of light and oxygen, to form benzaldehyde (x% of benzaldehyde is approximately equivalent to 1/3 *x*% of hydrogen peroxide). Hydrogen peroxide can rapidly oxidize sulfhydryl groups of amino acids such as cysteine present in peptides or proteins.

It is essential that adequate research and thought be given in the selection of a pharmaceutical excipient supplier. It is not uncommon for the supplier to change its manufacturing process to make products more efficiently (i.e., less costly). Normally, excipients are low-value, high-volume products that are used by several industries. The pharmaceutical industry, in general, is not the major customer of excipients (in terms of volume of material purchased). For example, the pharmaceutical industry uses approximately 20% of gelatin produced. Of this 20%, most is for production of oral dosage forms. The parenteral portion is approximately 5% of this 20%. Therefore, it is extremely important that the drug manufacturer has a contract with the excipient supplier, that prohibits the supplier from making any change in the process/quality of the material without informing their customers well in advance. Also, the pharmaceutical manufacturer should investigate all the alternate sources that could be used in case of an emergency. A change in the supplier should not be made without consulting the pertinent regulatory bodies, since such an event may require prior regulatory approval.

The pharmaceutical manufacturer should have an active Vendor Certification Program. The manufacturer also should assure that the vendor is ISO 9000 certified. An audit of the excipient manufacturer is essential, since the pharmaceutical industry is ultimately responsible for the quality of the drug product that includes the excipient(s) as one of the components. The IPEC GMP guide may be used as an audit tool, since it is written in the format of ISO 9000 using identical nomenclature and paragraph numbering. The audit may ensure that the quality is being built into the excipient that may be difficult to measure later by quality control on receipt of the material. This is especially true for parenteral excipients where not only chemical, but also microbiological attributes are critical. Bioburden and endotoxin limits may be needed for each of the excipients and several guidelines are available to establish the specifications (55, 56).

Recent events in Haiti highlight the importance of assuring the quality of excipients to the same degree that one normally does for active ingredients. From November 1995 through June 1996, acute anuric renal failure was diagnosed in 86 children. This was associated with the use of diethylene glycol-contaminated glycerin used to manufacture acetaminophen syrup (57).

SAFETY ISSUES

Reference 58 is an excellent resource on the safety and adverse reaction to several excipients. Sensitization reactions have been reported for the parabens, thimerosal,

and propyl gallate. Sorbitol is metabolized to fructose and can be dangerous when administered to fructose-intolerant patients. Table 13 also lists safety concerns.

Progress in drug delivery systems and new proteins/peptides being developed for parenteral administration has created a need to expand the list of excipients that can be safely used. An informational chapter included in the USP 24, presents a scientifically based approach for safety assessment of new pharmaceutical excipients (59). This chapter is based on the excipient safety evaluation guidelines prepared by The Safety Committee of the International Pharmaceutical Excipient Council, with appropriate redaction. Table 14 summarizes the approach in developing a new excipient.

Currently, there are some concerns regarding Transmissible Spongiform Encephalopathies (TSE) via animal-derived excipients such as gelatin. TSEs are caused by prions that are extremely resistant to heat and normal sterilization processes. TSEs have a very long incubation time with no cure and include diseases such as the following:

- Scrapies in sheep and goats
- Bovine spongiform encephalopathy (BSE), otherwise known as Mad Cow Disease, in cattle
- Kuru disease in humans
- Creutzfeld-Jacob disease (CJD) in humans, which has been attributed to repeated parenteral administration of growth hormone and gonadotropin derived from human pituitary glands.

Several guidelines have been issued that address the issue of animal-derived excipients and scientific principles to minimize the possible transmission of TSEs via medicinal products (60, 61). The current situation indicates that there are negligible concerns for lactose, glycerol, fatty acids, and their esters, but the situation is less clear for gelatin. In this scenario, if one has a choice, then it may be beneficial to select nonanimal-derived excipients. The use of bovine serum albumin (BSA) or human serum albumin (HSA) is of concern because they can be derived from virus-contaminated blood. The risk of TSEs from excipients can be greatly reduced by controlling the following parameters:

1. Source of animal should be from countries where BSE has not been reported.
2. Animals used should be young.
3. Category III or IV animal tissue should be used in manufacture (60).
4. A production process that is likely to destroy TSE agents should be utilized.

Table 14 Summary of safety evaluation of excipient

Tests	Injectable route[a]
Baseline toxicity data	
Acute oral toxicity	Required
Acute dermal toxicity	Required
Acute inhalation toxicity	Conditional
Eye irritation	Required
Skin irritation	Required
Skin sensitization	Required
Acute injectable toxicity	Required
Application site evaluation	Required
Phototoxicity/photoallergy	Required
Genotoxicity assays	Required
ADME/PK-intended route	Required
28-day toxicity (2 species) intended route	Required
Additional data: Short or intermediate term repeated use	
90-day toxicity (most appropriate species)	Required
Embryo-fetal toxicol	Required
Additional assays	Conditional
Genotoxicity assays	Required
Immunosuppression assays	Required
Additional data: Intermittent long-term or chronic use	
Chronic toxicity (rodent, nonrodent)	Conditional
Reproductive toxicity	Required
Photocarcinogenicity	Conditional
Carcinogenicity	Conditional

[a]Term injectable includes routes such as iv, sc, intrathecal, etc.

Amendment to the European Commission directive 75/318/EEC would require manufacturers to provide a "Certificate of Suitability" or the underlying "scientific information" in the form of a marketing variation to attest that their pharmaceuticals are free of TSEs.

FUTURE DIRECTION

Several new excipients are being evaluated in order to increase the solubility or improve the stability of parenteral drugs. Cyclodextrins have been tried for the above reasons. Currently, there are two FDA approved parenteral products that have utilized α and γ-cyclodextrins. β-cyclodextrin is unsuitable for parenteral administration because it causes necrosis of the proximal kidney tubules upon IV and subcutaneous administration (62). Hydroxypropyl β-cyclodextrin (HPβCD) and sulfobutylether β-cyclodextrin

(SBE-7-β-CD) have shown the most promise. Captisol™ is the trade name of SBE-7-β-CD and is anionic. Currently, two Captisol™ based small molecule IV and IM drug formulations are in Phase III clinical trials in the United States. One parenteral formulation that utilizes HPβCD (Cavitron®) is in Phase II/III clinical trials, and another (Sporanox) has been approved by the FDA. Manufacturers of HPβCD and SBE-7-β-CD have established a DMF with the FDA. A detailed review of cyclodextrins was recently published (63, 64). It should be noted, however, that cyclodextrin also can accelerate the degradation of drug product (65) and can sequester preservatives, rendering them ineffective (66).

Chitosan, β-1,4-linked glucosamine, is a naturally occurring, biodegradable, nontoxic polycationic biopolymer. It is being investigated for its potential as a cross-linked matrix of microspheres to deliver antineoplastic drugs. Because of its charge, it can trap several drugs and can bind strongly with cancer cells, thereby minimizing drug toxicity and enhancing therapeutic efficacy (67). Chitosan also has been shown to stabilize liposomes.

Biodegradable polymeric materials such as polylactic acid, polyglycolic acid, and other poly-alphahydroxy acids have been used as medical devices and as biodegradable sutures since the 1960s (68). Currently, the FDA has approved for marketing, only devices made from homopolymers or copolymers of glycolide, lactide, caprolactone, *p*-dioxanone, and trimethylene carbonate (69). Such biopolymers are finding increased application as a matrix to deliver parenteral drugs for prolonged delivery (70). At least four drug products—Lupron Depot®, Decapeptyl®, Nutropin Depot®, and Zoladex®—have been approved. These four drug products are microspheres in PLG, polylactic acid (PLA), or the PLGA matrix. Polyglycolic acid (PGA) is highly crystalline (approximately 50%) with a high melting point (220–225°C). PLA can be produced by the polymerization of L-lactic acid (LPLA), D-lactic acid (DPLA), or a blend of D- and L- lactic acid (DLPLA). LPLA is 37% crystalline while DLPLA, is amorphous. The degradation time of LPLA is much slower than that of DPLA requiring more than 2 years. By copolymerizing lactic and glycolic acid, polymeric matrices with a wide range of properties (tensile strength, crystallinity, and degradation rate) can be obtained. Decapeptyl® is approved in France and is a microsphere for IM administration. It contains drug in a matrix of PLGA and Carboxymethyl cellulose with mannitol and polysorbate 80.

Polyanhydrides degrade primarily by surface erosion and possess excellent in vivo compatibility. In 1996 the FDA approved a polyanhydride-based drug delivery system to the brain of chemotherapeutic agent BCNU, which is currently being manufactured by Guilford Pharmaceutical, Inc.

Several phospholipid-based excipients are finding increased application as solubilizing agents, emulsifying agents, or as components of liposomal formulation. The phospholipids occur naturally and are biocompatible and biodegradable. Examples include egg phosphatidylcholine, soybean phosphatidylcholine, hydrogenated soybean phosphatidylcholine (HSPC), DMPC, DSPC, DOPC, DSPE, DMPG, DPPG, and DSPG. Spartaject™ technology uses a mixture of phospholipids, to encapsulate poorly water-soluble drugs, to form micro-suspensions that can be injected intravenously. Busulfan® drug product uses this technology and is currently undergoing Phase I clinical trials. Many liposomal and liposomal-like formulations (DepoFoam®) are either approved (DepoCyt®) or are undergoing clinical trials to reduce drug toxicity, improve drug stability, prolong the duration of action, or to deliver drug to the central nervous system (71). Two amphotericin formulations have been approved in the United States, They are liposomal, or a lipid complex between the antifungal drug and positively charged lipid. Amphotec® is a 1:1 molar ratio complex of amphotericin B and cholesteryl sulfate while Abelcet® is a 1:1 molar complex of amphotericin B with phospholipids (seven parts of L-α-dimyristoylphosphatidylcholine and L-α-dimyristoylphosphatidyl glycerol).

Poloxamers or pluronics are block copolymers comprised of polyoxyethylene and polyoxypropylene segments. They exhibit reverse thermal gelation and are being tried as solubilizing, emulsifying, and stabilizing agents. Thus, a depot drug delivery system can be created using pluronics whereby the product is a viscous injection that gels upon IM injection (72). Pluronics can prevent protein aggregation or adsorption/absorption and can help in the reconstitution of lyophilized products. Pluronic F68 (Polaxamer-188), F38 (Poloxamer-108), and F127 (Poloxamer-407) are the most commonly used pluronics. For example, liquid formulation of human growth hormone and Factor VIII can be stabilized using pluronics. Fluosol® is a complex mixture of perfluorocarbons, with a high oxygen-carrying capacity emulsified with Pluronic F-68, and various lipids. It was recently approved by the FDA for adjuvant therapy to reduce myocardial ischemia during coronary angioplasty. A highly purified form of Poloxamer 188 (Flocor™), intended for IV administration, is undergoing Phase III clinical trials for various cardiovascular diseases. Purification of Poloxamer 188 has been shown to reduce nephrotoxicity.

Poloxamers and other polymeric materials such as albumin may coat the micro- or nano particle, alter their surface characteristics and reduce their phagocytosis and opsonization by the reticuloendothelial system following IV injection. Such surface modifications often result in prolongation in the circulation time of intravenously injected colloidal dispersions (73). Poloxamers also have been used to stabilize suspension such as NanoCrystal™ (74).

The first successful development of an injectable perfluorocarbon-based commercial product was achieved by the Green Cross Corporation in Japan, when it made Fluosol-DA®, a dilute (20% w/v) emulsion based on perfluorodecalin and perflurotripropylamine emulsified with potassium oleate, Pluronic F-68, and egg yolk lecithin. These perfluorocarbons are inert and also can be used to formulate nonaqueous preparations of insoluble proteins and small molecules (75). Perfluorocarbons also have been approved by the FDA for use in one ultrasound contrast agent, Optison®, which is administered via the IV route. Optison® is a suspension of microspheres of HSA with octafluoropropane. Heat treatment and sonication of appropriately diluted human albumin, in the presence of octafluoropropane gas, is used to manufacture microspheres in the Optison® injection. The protein in the microsphere shell makes up approximately 5–7 (wt%) of the total protein in the liquid. The microspheres have a mean diameter range of 2.0–4.5 μm with 93% of the microsphere being less than 10 μm.

Sucrose acetate isobutyrate (SAIB) is a high viscosity liquid system that converts into free-flowing liquid when mixed with 10–15% ethanol (76). On subcutaneous or IM injection, the matrix rapidly converts to a water-insoluble semi-solid, that is capable of delivering proteins and small molecules for a prolonged period. SAIB is biocompatible, and biodegrades to natural metabolites. This is a fairly new matrix and three INDs have been filed for veterinary applications. It has not been used in humans.

Several other biodegradable, biocompatible, injectable polymers are being investigated for drug delivery systems. They include polyvinyl alcohol, block copolymer of PLA–PEG, polycyanoacrylate, polyanhydrides, cellulose, alginate, collagen, gelatin, albumin, starches, dextrans, hyaluronic acid and its derivatives, and hydroxyapatite (77).

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